Thesis Title Effect of Pyridoxal Isonicotinoyl Hydrazone (PIH) Oral Iron Chelator, on Iron Absorption and Excretion : Animal and Human Studies.

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ABSTRACT

A number of new orally effective iron-chelating compounds has been developed for treatment of iron overload conditions. Acute and subacute toxicity test on these compounds suggested that pyridoxal isonicotinoyl hydrazone (PIH) has a very low toxic effect in both animals and man. From the clinical trial, six-day administration found the variation of urinary and fecal excretion which did not relate to iron store. This problem raised whether the iron-PIH complex was reabsorbed and redistributed to the organs, the effect of PIH on intestinal absorption of iron, and the relative effective dose of PIH compared to an equivalent effective dose of desferrioxamine (DFO).

A study on iron-PIH complex absorption and iron retention was performed using a rat model. Forty eight male Wistar rats weighing 168-350 g were grouped and individually housed in metabolic cages. The iron-PIH complex was prepared in the ratio of 1 : 2 and 1 : 1 in NSS : propylene glycol : ethanol in the ratio of 9 : 8 : 2. One μCi of ^{59}Fe was added per ml of solution per rat as tracer. The amount of iron fed was kept at 7.8 mg per rat. Results of the 7th

day radioiron retention were 25.8 ± 20.9 % in the control group (n = 23), 4.0 ± 1.2 % and 7.6 ± 4.5 % in the groups which received iron : PIH = 1 : 2 (n = 15) and 1:1 (n = 10), respectively. The fraction of total retained found in each organ did not vary significantly between the three groups.

Studies of the effect of PIH on iron absorption were performed in 6 patients with β-thal/HbE disease who were not regularly transfused and were in steady state. Two iron absorption measurements were performed in each patient using whole body counter. The first measurement was made after 600 mg of PIH had been taken along with radioiron ascorbate and 5 mg of carrier iron while the second measurement was made after administration of the radioiron and carrier iron without PIH. Results of the 14th day radioiron retention showed a significant inhibitory effect on GI iron absorption with the mean ± SD being decreased from 60.6 ± 4.0% to 28.8 ± 13.8 % of the administered dose.

To determine the clinical effectiveness of PIH, a study was made on 36 year old iron overload with β - thal/HbE volunteer who was not transfusion dependent. During the hospitalized period, a low iron diet was served. Twenty-four hours urine and stool were collected daily for iron analysis. Physical and blood examination were performed periodically. Each drug was administered for 6 days with 3 day resting interval. Either 600 mg PIH or placebo were administered orally at 6:00 a.m. 2:00 p.m. and 10:00 p.m. Ranitidine (150 mg) was given at 9:00 a.m. and 9:00 p.m. daily during the PIH and placebo administering period to prevent acid hydrolysis of the PIH. For the DFO period, 2 g/D was given subcutaneously for 10 hrs. Brilliant blue fecal marker (200 mg) were also taken with the first and the last dose of each drug. The iron excretion was found to be 0.37, 0.69, 26.44 through the urine and 4.26, 7.38, 10.66 mg Fe/D through the stool for placebo,PIH and DFO respectively.